AMENDMENTS TO THE SPECIFICATION

Please replace paragraphs **0093, 0102, 0103, 0133, 0138, 0144** and **0193** with the following amended paragraph(s). Deletions of original text are indicated with ~~strikethrough~~. Added text is shown underlined.

[0093] Cell lines which can be used in the methods of the present invention include, but are not limited to, those available from cell repositories such as the American Type Culture Collection (available on the internet ~~www.atcc.org~~), the World Data Center on Microorganisms (available on the internet ~~http://wdcm.nig.ac.jp~~), European Collection of Animal Cell Culture (available on the internet ~~www.ecacc.org~~) and the Japanese Cancer Research Resources Bank (available on the internet ~~http://cellbank.nihs.go.jp~~). These cell lines include, but are not limited to, the following cell lines: 293, 293Tet-Off, CHO-AA8 Tet-Off, MCF7, MCF7 Tet-Off, LNCap, T-5, BSC-1, BHK-21, Phinx-A, 3T3, HeLa, PC3, DU145, ZR 75-1, HS 578-T, DBT, Bos, CV1, L-2, RK13, HTTA, HepG2, BHK-Jurkat, Daudi, RAMOS, KG-1, K562, U937, HSB-2, HL-60, MDAHB231, C2C12, HTB-26, HTB-129, HPIC5, A-431, CRL-1573, 3T3L1, Cama-1, J774A.1, HeLa 229, PT-67, Cos7, OST7, HeLa-S, THP-1, and NXA. Additional cell lines can be obtained, for example, from cell line providers such as Clonetics Corporation (Walkersville, MD~~; www.clonetics.com~~). Optionally, the expressed RNA samples are derived from cultured cells optimized for the analysis of a particular disease area of interest, e.g., cancer, inflammation, cardiovascular disease, infectious diseases, proliferative diseases, an immune system disorder (e.g., multiple sclerosis, diabetes, allergy), or a central nervous system disorder (e.g., Alzheimer's ~~alzheimer's~~ disease, Parkinson's ~~parkinson~~ disease).

[0102] Permanent ~~Pemanent~~ genetic alteration can be produced by a variety of well known mutagenesis procedures, e.g., to generate mutant or variant cell lines suitable for library screening. A variety of mutagenesis protocols, such as viral-based mutational techniques, homologous recombination techniques, gene trap strategies, inaccurate replication strategies, and chemical mutagenesis, are available and described in the art.

These procedures can be used separately and/or in combination to produce modified cell lines for use in the methods of the present invention. See, for example, Amsterdam et al. "A large-scale insertional mutagenesis screen in zebrafish" Genes Dev 1999 Oct 13:2713-2724; Carter (1986) "Site-directed mutagenesis" Biochem. J. 237:1-7; Crameri and Stemmer (1995) "Combinatorial multiple cassette mutagenesis creates all the permutations of mutant and wildtype cassettes" BioTechniques 18:194-195; Inamdar "Functional genomics the old-fashioned way: chemical mutagenesis in mice" Bioessays 2001 Feb 23:116-120; Ling et al. (1997) "Approaches to DNA mutagenesis: an overview" Anal Biochem. 254(2): 157-178; Napolitano et al. "All three SOS-inducible DNA polymerases (Pol II, Pol IV and Pol V) are involved in induced mutagenesis" EMBO J 2000 Nov 19:6259-6265; and Rathkolb et al. "Large-scale N-ethyl-N-nitrosourea mutagenesis of mice--from phenotypes to genes" Exp Physiol 2000 Nov 85:635-44. Furthermore, kits for mutagenesis and related techniques are also available from a number of commercial sources (see, for example, Stratagene® ~~(http://www.stratagene.com/vectors/index2.htm)~~, Clontech™ ~~(http://www.clontech.com/retroviral/index.shtml)~~, and the Gateway® cloning system from Invitrogen™ ~~(http://www.invitrogen.com)~~. General texts which describe molecular biological techniques useful in the generation of modified cell lines, including mutagenesis, include Berger and Kimmel; Sambrook et al., and Ausubel et al., all *supra*. Further details regarding the generation of modified cell lines can be found in, e.g., WO 02/08466 by Monforte, and WO 01/71023.

[0103] Alternatively, procedures for making targeted gene mutations can be employed to modify cell lines prior to treating with members of a compound library. For example, a gene can be prevented from expressing any protein (knockout) via a number of processes, including deletion of the gene or transcription promoting elements for the gene at the DNA level within the cell. Knockout modifications generally involve modification of the gene or genes within the genome (see, for example, Gonzalez (2001) "The use of gene knockout mice to unravel the mechanisms of toxicity and chemical carcinogenesis" Toxicol Lett 120:199-208). Knockouts can be either heterozygous (e.g. inactivating only one copy of the gene) or homozygous (inactivating both copies of the gene). One exemplary database of

mouse knockouts can be found on ~~at http://research.bmn.com (~~the BioMedNet mouse knockout and mutation database~~)~~.

[0133] In a preferred embodiment, the array is a "chip" or "slide" composed, e.g., of one of the above specified materials, such as a glass microarray slide. Most commonly, nucleic acid samples corresponding to expressed RNA samples are deposited, e.g., "spotted" onto the chip or slide to produce a spatial array in which each distinct nucleic acid population corresponding to a different expressed RNA sample (e.g., derived from a different biological sample) is assigned a unique location on the microarray surface. Application of nucleic samples to the substrate can be performed using automated devices, or manually, for example, using a multipin, e.g., 32 pin, tool, with an alignment device (e.g., Xenopore, that can deposit up to 768 6 nl spots onto a glass slide). Detailed discussion of methods for linking nucleic acids to a substrate, are found in, e.g., US Patent No. 5,837,832 "Arrays of Nucleic Acid Probes on Biological Chips" to Chee et al., issued November 17, 1998; US Patent No. 6,087,112 "Arrays with Modified Oligonucleotide and Polynucleotide Compositions" to Dale, issued July 11, 2000; US Patent No. 5,215,882 "Method of Immobilizing Nucleic Acid on a Solid Substrate for Use in Nucleic Acid Hybridization Assays" to Bahl et al., issued June 1, 1993; US Patent No. 5,707,807 "Molecular Indexing for Expressed Gene Analysis" to Kato, issued January 13, 1998; US Patent No. 5,807,522 "Methods for Fabricating Microarrays of Biological Samples" to Brown et al., issued September 15, 1998; US Patent No. 5,958,342 "Jet Droplet Device" to Gamble et al., issued Sept. 28, 1999; US Patent 5,994,076 "Methods of Assaying Differential Expression" to Chenchik et al., issued Nov. 30, 1999; US Patent No. 6,004,755 "Quantitative Microarray Hybridization Assays" to Wang, issued Dec. 21, 1999; US Patent No. 6,048,695 "Chemically Modified Nucleic Acids and Methods for Coupling Nucleic Acids to Solid Support" to Bradley et al., issued April 11, 2000; US Patent No. 6,060,240 "Methods for Measuring Relative Amounts of Nucleic Acids in a Complex Mixture and Retreival of Specific Sequences Therefrom" to Kamb et al., issued May 9, 2000; US Patent No. 6,090,556 "Method for Quantitatively Determining the Expression of a Gene" to Kato, issued July 18, 2000; US Patent 6,040,138 "Expression Monitoring by Hybridization to High Density

Oligonucleotide Arrays" to Lockhart et al., issued March 21, 2000; NHGRI Microarray Project Protocols: on the internet at nhgri.nih dot gov, and further directed to: /DIR/Microarray/protocols.html ~~www.nhgri.nih.gov/DIR/Microarray/protocols.html~~; MacGregor P, Microarray protocol: on the internet at uhnres.utoronto dot ca, and further directed to: /services/microarray/download/protocols/procol_edward.pdf ~~www.uhnres.utoronto.ca/services/microarray/download/protocols/procol_edward.pdf~~; and Hedge et.al. (2000) Biotechniques 29: 548-562.

[0138] Typically, a moderate to large number of genes (i.e., expressed RNAs) are selected for analysis, i.e., expression (or response) profiling. Such a set of genes commonly includes at least three polynucleotide sequences, more commonly between about 10 and about 20 sequences, often about 50 sequences, sometimes about 100, and occasionally as many as about 1000, or more individual polynucleotide sequences, e.g., corresponding to different or distinct genes. Nucleic acid sequences that can be monitored in the methods of the present invention include, but are not limited to, those listed with the National Center for Biotechnology Information ~~(www.ncbi.nlm.nih.gov)~~ in the GenBank® databases, and sequences provided by other public or commercially-available databases (for example, the NCBI EST sequence database, the EMBL Nucleotide Sequence Database; Incyte's (Palo Alto, CA) LifeSeq™ database, and Celera's (Rockville, MD) "Discovery System"™ database). For example, nucleic acids that can be monitored (e.g., as part of the genetic response profile) according to the methods of the present invention include, nucleic acids encoding proteins including, but not limited to, signaling proteins, regulatory proteins, pathway specific proteins, receptor proteins, and other proteins involved in one or more biochemical pathways.

[0144] Multivariate statistics, such as principal components analysis (PCA), factor analysis, cluster analysis, n-dimensional analysis, difference analysis, multidimensional scaling, discriminant analysis, and correspondence analysis, can be employed to simultaneously examine multiple variables for one or more patterns of relationships (for a general review, see Chatfield and Collins, Introduction to Multivariate Analysis, published

1980 by Chapman and Hall, New York; and Höskuldsson Agnar, Predictions Methods in Science and Technology, published 1996 by John Wiley and Sons, New York). Multivariate data analyses are used for a variety of applications involving these multiple factors, including quality control, process optimization, and formulation determinations. The analyses can be used to determine whether there are any trends in the data collected, whether the properties or responses measured are related to one another, and which properties are most relevant in a given context (for example, a disease state). Software for statistical analysis is commonly available, e.g., from Partek® Inc. (St. Peters, MO~~; www.partek.com~~).

[0193] Numerous methods are known in the art for the amplification of nucleic acids in general and RNA specifically. Examples of amplification techniques include PCR, NASBA, TMA, RCA, as well as alternative amplification methods, e.g., as described in Puskas et al. (2002) Biotechniques 32:1330-1334; Eberwine (1996) Biotechniques 20: 584-591; Van Gelder et al. (1990) Proc Natl Acad Sci USA 87:1663-1667; and in United States Patents Numbers: 6,251,639, ~~6,~~ 5,962,271 and 5,545,522. The majority of these methods can be used for either global amplification of nucleic acids, e.g. using random priming and/or poly T priming, or specific amplification using gene or gene family targeted priming.